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Puberty in 24 Patients with Klinefelter Syndrome

E. Topper[1], Z. Dickerman[1], R. Prager-Lewin[1], H. Kaufman[2], Z. Maimon[3], and Z. Laron[1]

[1] Institute of Pediatric and Adolescent Endocrinology, the [2] Steroid and [3] Cyto-Genetic Laboratories, Beilinson Medical Center, Petah Tikva and the Sackler School of Medicine, Tel Aviv University, Israel

Abstract. Twenty four boys with Klinefelter syndrome, 18 of whom were diagnosed prepubertally, were observed until adulthood. Onset of puberty, as judged from testicular enlargement and pubic hair development, occurred between 11 to 14 years in the above 18 patients. By the age of 17 pubic hair, penile length and height had reached the adult stage in all patients, but arrest of testicular growth was noted at mid-puberty, 13 years, with maximal mean (± SD) volume attained being 3.5 ± 1.5 ml. The first conscious ejaculation was reported to have occurred between 13 to 16 years in 10 patients and in the remaining 4 between 17 to 18 years of age. Sperm counts obtained after the age of 18 revealed azospermia or severe oligospermia in all patients except one, who had a sperm count of 30×10^6/ml. The hypothalamic-pituitary-gonadal axis, assessed by LH-RH and hCG stimulation tests, was found to be normal in prepuberty and during early pubertal stages. From mid-puberty the basal levels of plasma FSH and the response to LH-RH showed a gradual increase above the normal. Towards late puberty (>15 years) basal and peak levels of LH were above normal with a concomitant decrease in the basal level of testosterone and its response to hCG.

These findings indicate that during childhood and early puberty function of the hypothalamic-pituitary-gonadal axis is normal in Klinefelter syndrome, allowing the onset of pubertal signs at the appropriate age, and that until late puberty there is a relative preservation of function in the testicular Leydig cells, permitting the normal sequential development of the androgen-dependent pubertal signs. The measurement of testicular testosterone reserve by means of hCG stimulation constitutes a useful aid in determining when and if testosterone replacement therapy should be instituted.

Key words: Klinefelter syndrome – Puberty

The clinical, hormonal and histological picture of Klinefelter syndrome has been given wide attention in the literature since the original description published in 1942 [13]. Histological studies indicate that testicular damage is already present in the perinatal and prepubertal periods [15, 21]. The progression of these changes during puberty has been found to lead to faulty spermatogenesis [10] as well as a decrease in testosterone production and secretion by the testes [14, 31] with signs of hypovirilization in most of these patients [8].

Reprint requests to: Prof. Z. Laron, Institute of Pediatric and Adolescent Endocrinology, Beilinson Medical Center, Petah Tikva 49 100, Israel

Presented here are the findings made during long-term follow-up in 24 patients with Klinefelter syndrome, most of whom had been diagnosed before puberty. It was the aim of this study to investigate the sequence of the clinical and hormonal changes taking place and their inter-relationships, before and during puberty.

Patients and Methods

The patient material comprised 24 patients in all of whom the diagnosis of Klinefelter syndrome was confirmed by chromosomal studies. In 18, diagnosis was made before the age of 13 years so that they could be followed throughout puberty into adulthood. All patients underwent a complete physical examination at least once a year. The pubertal stages were assessed according to Tanner's criteria for pubic hair development [33] and skeletal age according to the Atlas of Greulich and Pyle [9].

In all patients the hypothalamic-pituitary-gonadal axis was evaluated at various pubertal stages by means of LH-RH and hCG tests. FSH and LH were measured by double antibody radioimmunoassay (RIA), as described by Midgley [23, 24]. For the hLH RIA system LER 960 was used for iodination. For the hFSH RIA system LER 1366 was used for iodination. The anti hLH serum was batch No. 1 NPA and the anti hFSH serum was batch No. 3 NPA. Results are expressed in mU of LH or FSH per ml of plasma, LER 907 serving as a reference preparation. The biological potency of 1 mg is 20 IU of FSH and 48 IU of LH. Plasma testosterone was measured by RIA, with some modification of the method of Weinstein et al. as described by Laron et al. [18]. LH-RH tests were performed after an overnight fast on an ambulatory basis by injecting synthetic LH-RH (Ferring, Sweden) 50 mcg/m^2 i.v. in one bolus, measuring the FSH and LH in plasma samples taken before injection and 15, 30, 45, 60 and 90 min after LH-RH administration. The hCG test was performed with a single intramuscular injection of 5000 IU hCG (Chorygon-Ikapharm, Israel), measuring the plasma testosterone before and on the 3rd and 4th days followeing injection of hCG [12]. The volume measurement of seminal fluid and a sperm count were made in patients over the age of 18 years, the fluid being obtained by masturbation. In the 4 patients who had been receiving testosterone, the tests were performed 3 months or more after discontinuation of this replacement therapy.

Statistical analysis was made using the Student's *t*-test.

Informed consent was obtained from all patients or, if they were minors, from their parents before performance of the tests.

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Table 1. The pertinent clinical data of 24 boys with Klinefelter's syndrome at referral

No.	Name	CA (years)	B.A.	Follow-up (years)	T.V. (ml)		P.L. (cm)	P.H. (T)	Height		Span (cm)	U/L ratio	Sub.S. S.F. mm
					Rt.	Lt.			cm	Perc.			
1	B. M.	5	5	14	1	–[a]	5.8	1	116	90	113	1.2	11
2	Y. B.	5½	3½	13.5	–[a]	2	5.2	1	119.5	92	120	1.2	8
3	O. O.	6	5	13	1.5[b]	1.5[b]	5.4	1	121.5	90	117.5	1.2	6
4	H. O.	6	3	12.5	2	–[a]	5.0	1	110	10	110	1.2	13
5	A. G.	6	6½	16	1[a]	1	4.0	1	126	97	125	1.2	7
6	M. Z.	6½	4	13.5	1[a]	0.5[a]	4.0	1	121	75	128	1.1	10
7	S. H.	6½	5	13.5	1[a]	2	4.3	1	113	10	120	1.2	12
8	E. E.	7½	7½	11	2	1[a]	4.0	1	132	97	133	1.2	10
9	Y. F.	9	9	9.5	1[b]	1[b]	6.0	1	135.5	90	135	1.1	11
10	M. M.	9½	13½	9	1	1.5	3.5	1	145	97	145	1.2	8
11	D. G.	10	10	10	1[b]	1	5.2	1	153	97	150	1.1	13
12	Y. A.	10	9	12	1	2	4.8	1	146.5	90	147	1.1	27
13	I. B.	11	10½	8	2[b]	2[b]	5.3	1	147	75	142	1.0	6
14	O. A.	11	13½	11.5	2	2	4.5	2	152	90	152	1.0	9
15	M. S.	11	10	8.5	0.5[a]	0.5	4.5	1	140	50	136	1.0	13
16	E. S.	11	13	8	4	4	8.4	4	164.2	+3 SD	164	1.2	8
17	R. D.	12	9½	7	1.5[b]	1.5[b]	5.6	1	152	90	152	1.0	10
18	Y. P.	13	10½	6	–[a]	5	8	2	162	80	160	1.0	12
19	D. C.	16	15	3	3	3	13	3	178.6	75	174	1.0	12
20	S. E.	16	16	7	4	4	13	4	178	80	180	1.0	35
21	I. L.	16½	17	3	2	2	11	5	186	95	184	1.0	18
22	Z. B.	17½	18	6.5	4	4	12	5	175	50	172.5	1.0	13
23	I. S.	18	18	3	3	3	10.5	5	181	80	176	1.0	10
24	N. O.	25	18	3	2.5	2.5	13	5	186	90	180	1.0	11

CA = chronological age; BA = bone age (ref. No. 9); T. V. = testicular volume; P.L. = penile length (cm); P.H. = pubic hair (ref. No. 33); U/L ratio = the ratio between the upper and lower body segments (ref. No. 1); Sub.S. S.F. = Sub scapular skin fold
[a] = Undescended testes; [b] = mobile testes

Results

Clinical Findings

Fourteen of the 3216 boys with undescended or mobile testes referred to our Institute in the years 1960–1977, were diagnosed as cases of Klinefelter syndrome on the basis of a routine buccal smear for sex chromatin [17]. An additional 10 boys were discovered to have Klinefelter syndrome following their referral because of hypogonadism (testicular volume less than 1.5 ml in prepuberty) in 3, gynecomastia in 3, hypogenitalism in 3 and tall stature in one patient respectively. The clinical data at admission of these patients, are summarized in Table 1.

Onset of puberty, as indicated by pubic hair development, was observed before the age of 12 years in 2 of 17 patients and before the age of 14 years in 12 of 18 patients (Table 2). By the age of 17, pubic hair development had reached the adult stage in all patients. Testicular enlargement was noted before the age of 12 years in one patient and before the age of 14 years in 9 patients (Table 2).

The maximal testicular volume with a mean (±SD) of 3.5±1.5 ml was reached at about the age of 13 years (Table 2, Fig. 1). Penile growth was observed to start between 12–13 years of age, reaching a maximal length between 16–17 years of age,

Table 2. Pubertal signs – sequential development in patients with Klinefelter's syndrome

	Age (years)			
	≦12	13–14	15–16	17
	N			
	17	18	20	24
Testicular volume (ml)				
2.5	16	8	2	1
3–4	–	9	17	21
5–8	1	1	1	1
Pubic hair (T[a])				
I	15	4	–	–
II	1	13	4	–
III	1	–	3	–
IV	–	–	7	–
V	–	1	6	24
First conscious ejaculation[b]		7	20	24

[a] Tanner's criteria for pubic hair development
[b] According to patient's statement

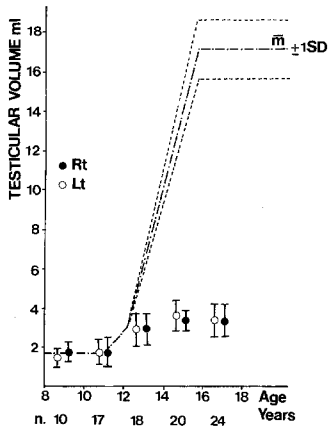

Fig. 1. Mean testicular volume (±SD) in boys with Klinefelter's syndrome on longitudinal follow-up

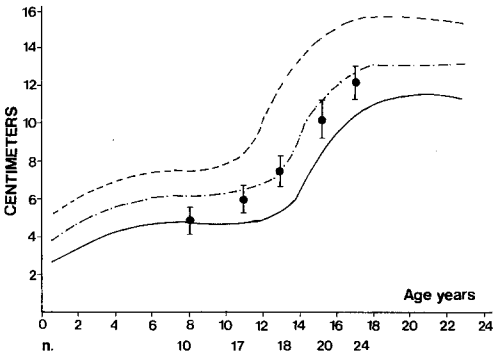

Fig. 2. Mean penile length (± SD) in boys with Klinefelter's syndrome on longitudinal follow-up

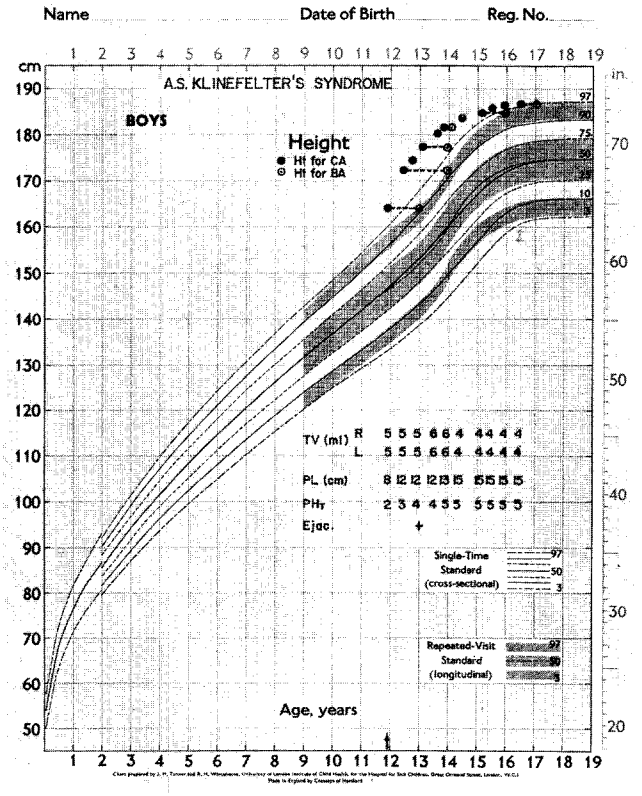

Fig. 3. Early growth acceleration and pubertal development in a boy with Klinefelter's syndrome. At the age of 12 years the testicular volume was 5 ml and pubic hair was P_3. First conscious ejaculation appeared at the age of 13 years

with a mean (±SD) of 12±1 cm (Fig. 2). Growth velocity was found to be maximal at the age of 13 years, when it was 9± 3.5 cm/years. The first conscious ejaculation was reported to have occurred between the age of 13–14 years in 7 patients, between 15–16 years in 13, and in the other 4 at age 17 or later (Table 2). Body proportions judged from the ratio of upper to lower segments of the body, were normal in all patients [1]. Except for the undescended or mobile testes (Table 1) no other genital or scrotal anomalies were found.

In one patient (E.S., No. 16) there was an unusual clinical picture for this syndrome. He was referred at the age of 11 years because of accelerated growth and tall stature and during follow-up he showed a rapid progression of the androgen-dependent signs despite the arrest of testicular growth at a volume of 6 ml (Fig. 3).

In 4 patients (Nos. 21–24) a long acting testosterone preparation was given from the age of 17 years, since testosterone levels were found to be less than 300 ng/dl.

Laboratory Findings

In 23 patients the karyotype was 41 XXY and in one (S. H., No. 7) there was a 47 XXY/48 XXYY mosaicism. Up to the age of 12 years the mean basal plasma LH and FSH levels were found to be within the range of the normal matched-for-age controls (Table 3). Above age 13, the mean basal plasma FSH levels were significantly ($P<0.001$) higher than normal levels and beyond age 15 the mean basal plasma LH levels were also significantly ($P<0.001$) higher than normal. Up to the age of 12 years the mean peak responses of plasma FSH and LH to synthetic LH-RH stimulation were normal in most patients although in a few they were already elevated before the age of 13; after the age of 13 years they were significantly higher in all patients ($P<0.001$). Before the age of 14 years, basal plasma levels of testosterone were within the normal range and between 14 to 16 years they were within the low normal range. After this age they were significantly ($P<0.01$) lower than normal. Before the age of 12 years, the mean peak plasma testosterone response to hCG stimulation was within the normal range but after this age it was lower than normal.

Twenty-three patients had a spermatogram showing either azospermia or severe oligospermia ($0-6\times10^6$ cells/cm^3), with the volume of ejaculate being 0.5–1.5 ml. One patient (No. 17) had a sperm count of 30×10^6 and an ejaculate volume of 2 ml. This patient later married and fathered a child as reported in details elsewhere [20].

Discussion

All of the Klinefelter syndrome patients in this study were observed to have a normal onset of puberty, as judged by the appearance of the pubic hair as well as the testicular enlargement prior to the age of 14 years. All of the androgen-dependent pubertal signs, including sexual hair, penile growth and growth velocity, showed normal development. The first conscious ejaculation occurred as would normally be expected [19]. Towards mid-puberty, however, there was an evident arrest of testicular growth, probably due to fibrosis and hyalinization of the seminiferous tubules [2, 3, 16, 26] and subsequently the testes even diminished in size. This was accompanied by a decrease in or complete lack of spermatogenesis, one of the main characteristics of this syndrome [4], with all but one patient having azospermia or severe oligospermia.

Table 3. Plasma FSH and LH response to LH-RH test (50 mcg/m^2 i.v.) and plasma testosterone response to hCG (5000 IU i.m.) in patients with Klinefelter syndrome

Age (years)		LH-RH test				hCG test	
		FSH mIU/ml		LH mIU/ml		Testosterone ng/dl	
		Basal	Peak	Basal	Peak	Basal	Peak
	N	6 (10)	5 (10)	6 (10)	5 (10)	5 (11)	5 (11)
5-10	M±SD	0.9± 0.3	3.2± 0.9	0.54± 0.2	1.9± 0.9	13.3± 10.0	94.5± 54.6
	Range	0.5− 1.0	2.0− 4.6	0.2 − 0.8	0.4− 2.6	6.2− 26	80.0− 137
	Normal	0.6± 0.2	1.5± 0.5	0.5 ± 0.1	1.3± 0.2	18.0± 9	127.0± 27
	Control	0.5− 0.8	1.0− 3.0	6.2 − 1.0	0.6− 1.8	6.0− 31	95.0− 172
	N	5	4	5	5	3	3
11-12	M±Sd	1.0± 0.6	2.6± 1.4	0.8 ± 0.2	3.7± 1.7	29.4	169.5
	Range	0.5− 1.8	0.7− 4.0	0.6 − 1.2	0.9− 5.6	6.2− 32	82.5− 137.5
	N	5 (10)	5 (10)	6 (10)	5 (10)	5 (5)	3 (5)
13-14	M±SD	2.2± 0.8	3.9± 1.3	1.2 ± 0.6	8.7± 5.4	108.5± 28.2	185
	Range	1.2− 3.3	2.8− 8.6	0.6 − 2.2	2.9−15.1	80.0−138	112.0− 130
	Normal	1.0± 0.4	2.4± 0.9	0.8 ± 0.1	5.9± 0.4	68.0± 18	452.0± 150
	Control	0.5− 1.8	1.3− 4.7	0.6 − 1.2	4.5− 7.5	43.0−112	275.9− 680
	N	7 (10)	7 (10)	7 (10)	7 (10)	6 (7)	6 (7)
15-16	M±SD	13.2± 6.0	31.3±10.0	4.2 ± 1.7	21.7	141.6± 97.2	358.4± 171.1
	Range	4.7−27.4	21.0−40.0	2.2 − 6.9	13.4−25	38.0−238	250.0− 650
	Normal	2.8± 0.8	3.0± 1.0	1.3 ± 0.2	14.9± 2.3	287.0± 60	1200.0± 350
	Control	1.0− 3.4	2.3− 4.3	0.6 − 2.4	7.2−24	178.0−375	702.0−1600
	N	15 (10)	6 (10)	14 (10)	7 (10)	15 (8)	5 (8)
>16	M±SD	23.9± 9.8	25.8±12.2	11.0 ± 6.7	29.2± 7.3	179.5± 83	300.4± 139.9
	Range	5.7−40	25.0−35.0	3.2 −23.8	25.0−40	64.0−325	150.0− 510
	Normal	2.6± 1.0	4.5± 1.6	1.9 ± 0.4	14.2± 2.2	470.0± 75	1200.0± 204
	Control	1.0− 3.9	1.6− 8.6	0.5 − 4.0	7.6−23	359.0−660	890.0−1600

( )=Numbers in parenthesis represent normal controls

Thus there was an evident dissociation between the normal progression of the androgen-dependent pubertal signs and testicular development. This clinical manifestation was reflected in the tests for function of the hypothalamic-pituitary-gonadal axis. In prepuberty LH-RH and hCG tests indicated normal functioning which permitted the normal onset of puberty. Towards mid-puberty the exaggerated response of FSH to LH-RH and the subsequent rise in basal levels of FSH indicated a progressive failure of the negative feedback mechanism which regulates this hormone, probably due to dysfunction of the seminiferous tubules which is thought to be related to a lack of inhibin [11, 28, 30, 32]. It has been suggested that the prolonged elevation of FSH secretion demonstrated in patients with Klinefelter syndrome may accelerate the primary process of fibrosis and hyalinization of the seminiferous tubules [4]. The normal basal levels and responses of LH and the normal testosterone found at this stage indicate preservation of Leydig cell function [6, 7, 22, 34], which permits the normal development of the androgen-induced pubertal signs. Similar clinical and laboratory results were published recently by Salbenblatt et al. [29]. The gradual increase in plasma LH levels found from mid-puberty onwards may represent a compensatory effort to maintain Leydig cell function which is successful in bringing the virilization process to the adult stage. It is only in late puberty, from the age of 17 onwards, that the gradual decrease in plasma testosterone and the response to hCG provide evidence of the ultimate failure of Leydig cell function and the possible need for replacement therapy.

In the present study the presenting symptoms and physical findings did not differ from those previously reported by others [10] with the exception that none of our patients showed eunochoid body proportions [25] or genital anomalies such as hypospadias [27].

Our study indicates that there is a higher prevalence of Klinefelter syndrome among boys with cryptorchidism or mobile testes, i.e. 1/229 vs. 1/450-600 male neonates (5, 10]. In 16 (70%) of the 24 patients the diagnosis of Klinefelter syndrome was made before puberty on the basis of the routine buccal smear taken for determination of sex chromatin in boys with undescended or mobile testes [17, 20] or hypogonadism. These findings again emphasize the importance of using this simple test routinely in such patients.

In view of the evidence provided by this study of the functional failure which eventually occurs despite the normal onset

and progression of pubertal signs, it is suggested that the measurement of testicular testosterone reserve by means of hCG stimulation constitutes a useful aid in determining when and if testosterone replacement therapy should be instituted.

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